Characterization of 1q Duplication by Array Comparative Genomic Hybridization in Acute Myeloid Leukemia Patients with t(8;16)(p11.2;p13.3)

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Research

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Abstract

Background: Acute myeloid leukemia (AML) is a complex hematological disease characterized by genetic and clinical heterogeneity. The identification and understanding of chromosomal abnormalities are important for the diagnosis and management of AML patients. Compared to recurrent chromosomal translocations in AML, t(8;16)(p11.2;p13.3) can be found in any age group, but is very rare and typically associated with poor prognosis.

Methods: Cytogenetic studies were performed among 1,824 AML patients from our oncology database in the last 20 years by karyotype analysis. Fluorescence in situ hybridization (FISH) was used to further confirm the chromosomal translocation fusion. Array comparative genome hybridization (aCGH) was carried out to characterize the additional chromosomal segments in patients with t(8;16)(p11.2;p13.3).

Results: Three patients with t(8;16)(p11.2;p13.3) were identified. One patient was pure t(8;16)(p11.2;p13.3), and the other two had an additional chromosomal anomaly of 1q duplication. Interestingly, the molecular size and position of this 1q duplication were similar in both patients, showing as 46.7 Mb and 49.9 Mb, respectively.

Conclusion: 1q duplication is a recurrent event in AML patients with t(8;16)(p11.2;p13.3), indicating it could also play a role of an unfavorable prognostic factor.

Background

Acute myeloid leukemia (AML) is a common disease characterized by immature myeloid cell proliferation and bone marrow failure, which can be subdivided into 9 to 11 pathogenetically different subtypes [1]. Over the past two decades, the incidence rate has increased by 30% [2, 3]. Furthermore, AML has a poor long-term survival with a high relapse rate [4]. So, AML represents a substantial health problem that requires strict monitoring and innovative treatment strategies, and needs the development of newer effective treatment strategies in AML.

To present, detection of cytogenetics and mutation has been regarded as a critical prognostic tool for AML treatment [5]. Byrd et al. (2002) Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with *de novo* AML [6]. Hence, it is intensively necessary to identify chromosomal rearrangements in AML patients and provide whole spectrum of cytogenetic abnormalities for AML. According to the World Health Organization classification updated in 2008, AML with recurrent genetic abnormalities including t(8;21)(q22;q22), t(11q23)/*MLL*, t(15;17)(q24;q21), inv(16)(p13.1q22), and t(16;16)(p13.1;q22) were identified [7, 8]. Non-random chromosomal abnormalities such as deletions, translocations are reported to be detected in approximately 52% of all adult AML patients. Furthermore, chromosomal abnormalities have been recognized as the genetic events which can cause and promote this disease [9]. Certain cytogenetic abnormalities, including the t(8;21)(q22;q22), t(15;17)(q24;q21) and inv(16)(p13.1;q22) are shown to be associated with longer remission and survival, while alterations of chromosomes 5, 7, 11q23 and

complex karyotypes are associated with poor response to therapy and shorter overall survival [10]. Chromosomal translocations as t(15;17)/*PML-RARA*, t(8;21)/*RUNX1-RUNX1T1*, inv(16)/*CBFB-MYH11* and t(11q23)/*MLL* are usually found in AML patients [11, 12]. However, AML with t(8;16)(p11.2;p13.3) is a very uncommon AML subtype, and this AML subtype can be found in any age group, from newborn to the eighth decade of life, with a female predominance [13–17]. A majority of adult patients with t(8;16)(p11.2;p13.3) are therapy related [14–17], and pediatric patients tend to be *de novo* [13]. There are approximately 160 cases reported in works of literatures [13–17], and the first t(8;16)(p11.2;p13.3) in an infant was described in 1983 [18]. Some AML patients with t(8;16) (p11.2;p13.3) have a bleeding tendency and disseminated intravascular coagulopathy, which is overlapping clinical features that mimic acute promyelocytic leukemia (APL) [17]. Unlike APL, AML with t(8;16)(p11.2;p13.3) has unfavorable treatment and outcome [14, 19]. As a sole chromosomal anomaly, t(8;16)(p11.2;p13.3) is found in more than 50% of reported cases, and one or more additional chromosomal anomalies can be seen in the remaining cases [20]. The most common secondary chromosomal anomalies are found to be trisomy 8 or partial trisomy 8, and monosomy 7 or deletion of the long arm or short arm of chromosome 7[13–16, 19]. Comparatively, the gain of 1q in variable sizes were also frequently noticed in patients with t(8;16)(p11.2;p13.3) in these large studies [13–15, 19].

Recurrent cytogenetic abnormality t(8;16)(p11.2;p13.3)/*KAT6A-CREBBP* is seldom associated with AML, and the 1q duplication in AML patients with t(8;16)(p11.2;p13.3) has never been discussed. In the present study, a total of 1,824 *de novo* or treatment-related AML patients were collected from our laboratory oncology database. Among them, three patients were t(8;16)(p11.2;p13.3), including one was pure, and the other two had additional chromosome anomalies with a 1q duplication characterized by array comparative genome hybridization (aCGH).

Methods

Patients

This study was approved by the Institutional Review Board (IRB) of Oklahoma University (IRB Number: 2250). A total of 1,824 AML patient samples were studied cytogenetically from 2000 to 2019 at the Genetics Laboratory of Oklahoma University Health Sciences Center. Bone marrow samples were obtained from three of the 1,824 patients who had t(8;16)(p11.2;p13.3).

Conventional cytogenetic analysis

Short-term cultures of unstimulated bone marrow samples were set up and harvested according to the standard laboratory protocols. Karyotype analysis was performed using giemsa and trypsin technique for G-banding. The cytogenetic abnormalities were described according to the International System for Human Cytogenetic Nomenclature (ISCN 2016).

Fluorescence in situ hybridization analysis

Fluorescence in situ hybridization (FISH) assayswere performed according to the manufactures' instruction in combination with our established laboratory protocols. The PML/RARA dual-color, dual-fusion translocation probe (Abbott Molecular Inc., Des Plaines, IL, USA), the sub-telomere specific probes for chromosome 3 p-arm and q-arm, and the whole chromosome painting (WCP) probes for chromosome 1, 3 and 14 were purchased from Cytocell Ltd, NY, USA. A spectrum green-labeled probe mapping to the 8p11.21 region and a spectrum orange-labeled probe mapping to the 16p13.3 region was created in house, respectively with the following BAC/PAC clones: RP11-642I24[chr8: 41,676,336-41,856,494(hg19)] and RP11-589C21[chr8: 41,873,702-42,036,222(hg19)], RP11-619A23[chr16: 3,720,076-3,914,571(hg19)] and RP11-95J11[chr16: 3,860,374-4,025,510(hg19)] (Children's Hospital Oakland Research Institute, Oakland, CA, USA). The KAT6A gene located on 8p11.21 and the CREBBP gene located on 16p13.3 was covered by the green-labeled and red-labeled home-brewed probe, respectively. All probes were validated before use. Chromosome spreads were counterstained with 4,6-diamidino-2-phenylindole (DAPI4) in an antifade medium (Vector Laboratories Inc., CA, USA). Digital images carrying specific hybridization signals were captured and processed on CytoVision version 7.0 (Applied Spectral Imaging, Carlsbad, CA, USA).

aCGH analysis

Genomic DNA was extracted from each three patient's bone marrow pellet according to the standard operating procedure using the phenol and chloroform method with a commercially-available DNA extraction kit (Puregene blood kit, Qiagen, Valencia, CA) or Nucleic Acid Isolation System (QuickGene-610L, FUJIFILM Corporation, Tokyo, Japan). Two aCGH platforms including NimbleGen and Agilent were used in this study. For the NimbleGen aCGH platform, human reference genomic DNA was purchased from Promega Corporation (Promega Corporation, Madison, WI, USA). The patient's DNA and the reference DNA were labeled with either Cyanine 3 (Cy-3) or Cyanine 5 (Cy-5) by random priming, and then equal quantity of both labeled products were mixed and loaded onto a 720 K oligonucleotide chip (Roche NimbleGen Inc., Madison, WI, USA) to hybridize at 42°C for 40 h in a MAUI hybridization system (BioMicro Systems, Salt Lake City, UT) according to the manufacturer's protocols with minor modifications. The slides were washed with washing buffers (Roche NimbleGen Inc.) after hybridization and scanned using Roche Scanner MS200 (Roche NimbleGen Inc.). Images were analyzed using software from NimbleScan software version 2.6 and the SignalMap software version 1.9 (Roche NimbleGen Inc.). The genomic positions were determined using GRCh36/hg18, UCSC Genome Browser. For the Agilent aCGH platform, human reference genomic DNA was purchased from Agilent Corporation (Agilent Corporation, Santa Clara, CA, USA). The patient's DNA and the purchased reference DNA were labeled with either cyanine 3 (Cy-3) or cyanine 5 (Cy-5) by random priming (Agilent Corporation). Patient DNA (labeled with Cy-3) was combined with a normal control DNA sample (labeled with Cy-5) of the same sex and hybridized to an Agilent 2 × 400 K oligo microarray chip (Agilent Technologies) by incubating in Agilent's Microarray Hybridization Ovens (Agilent Technologies). After a 40 h of hybridization at 67°C, the slides were washed

and scanned using the NimbleGen MS 200 Microarray Scanner (Roche NimbleGen Inc.). Agilent's CytoGenomics 2.7 software (Agilent Technologies.) was applied for data analysis. The genomic positions were determined using GRCh37/hg19, UCSC Genome Browser.

Results

Data of patients

The information and routine cytogenetic findings of patients were listed in Table.1. Three patients with t(8;16)(p11.2;p13.3) were identified from a total of 1,824 AML patients in our laboratory's oncology database using karyotype analysis. Patient No.1 was an 82 years old male referred to us for evaluation of anemia. Patient No.2 was a 28 years old female presented with disseminated intravascular coagulopathy at admission and then excluded for APL based on the negative result of rapid FISH for t(15;17)(q24;q21)/*PML-RARA* (data not shown). Patient No.3 was a 69 years old female who referred to us for evaluation of AML (not APL) developed after treatment for breast cancer. Flow cytometric analysis on patient No.2 and No.3 noted approximately 57% and 69% monocytic cells, respectively, supporting the diagnosis for AML with monocytic differentiation (subtype M5).

Analysis Of T(8;16) Patients Using Karyotyping, Fish And Acgh

Routine chromosome analysis on patient No.1 demonstrated a translocation between short arms of chromosome 8 and 16 at bands 8p11.2 and 16p13.3 (Fig. 1a). Karyotype analysis of patient No.2 revealed the chromosomes rearrangement t(8;16)(p11.2;p13.3) and additional material attached to the short arm of chromosome 14, which might be part of the long arm of chromosome 1(Fig. 1b). Additionally, the t(8;16)(p11.2;p13.3) and a similar additional chromosomal material attached to the long arm of chromosome 3 were found in patient No.3 (Fig. 1c). The patient's karyotype was 46, XY, t(8;16)(p11.2;p13.3)[17]/46,XY[3] (patient No.1), 46, XX, t(8;16)(p11.2;p13.3), add(14)(p11.2)[11]/46,XY[9] (patient No.2) and 46, XX, t(8;16)(p11.2;p13.3)[2]/46, idem, add(3)(q?27)[18] (patient No.3), respectively. Then, the male patient with a pure t(8;16)(p11.2;p13.3) was excluded for further aCGH investigation. The remaining two female patients had t(8;16)(p11.2;p13.3) with the additional chromosomal anomalies of 1q were detected by subsequent FISH and aCGH.

The translocation t(8;16)(p11.2;p13.3) disrupts the *KAT6A* gene on 8p11.2 and the *CREBBP* gene on 16p13.3, resulting in the fusion of these two genes. In order to confirm the translocation between chromosome 8 and 16 on patient No.2 and No.3, we set up FISH studies using home-brewed probes corresponding to the *KAT6A* gene and the *CREBBP* gene. As we expected, the analyzed metaphase cells of these two patients exhibited the same abnormal hybridization pattern on these two patients: two yellow abnormal fusion signals involving one on the derivative chromosome 8 and another on the derivative chromosome 16 (Fig. 2a and b). In addition, we performed FISH analysis in patients No.2 and

No.3 using WCP 1 and 14, WCP 1 and 3 FISH probes, respectively. Metaphase cells were observed and manifested that the extra chromosomal materials on chromosome 14 chromosome 3 were both from chromosome 1 (Fig. 2c and 2d). Moreover, we used the sub-telomere specific FISH probes on chromosome 3 p-arm and q-arm for patient No.3 and confirmed no loss of the end portion of the long arm of chromosome 3, and the extra material was also indicated (Fig. 2e).

aCGH assay was carried out to determine the chromosomal origin of the additional materials attached to chromosome 14 and chromosome 3. A partial duplication of chromosome 1 long arm at bands q32.1q44 (201,304,064–248,102,389 bp, GRCh36/hg18, USCS Genome Browser), and bands 1q32.1q44(201,408,592 – 251,323,872 bp, GRCh37/hg19, UCSC Genome Browser), was indicated in patient No.2 and No.3, respectively. The molecular size of the duplication region was 46.7 Mb for patient No.2 and 49.9 Mb for patient No.3. No patient had copy number variants on the remaining chromosomes (Fig. 3).

Discussion

AML is one of the most common diseases characterized by proliferation of blast cells in bone marrow or peripheral blood, which accounts for approximately 30% of leukemia adult cases. Based on cytogenetic and molecular analysis, the efficiency of AML diagnosis has largely promoted over the past 15 years, making the characterization of this disease easier [5]. As reported previously, the chromosomal anomaly including karyotype aberrations, gene mutations, and gene expression abnormalities is often observed in AML patients. Recurrent chromosomal translocations such as t(8;21), t(15;17), and inv(16) are frequently detected, but numerous other uncommon chromosomal aberrations in AML also exist [12]. The identification of fusion transcripts such as t(8;21)(q22;q22)/*RUNX1-RUNX1T1*, inv(16)(p13.1;q22)/*CBFB-MYH11* or t(15;17)(q24;q21)/*PML-RARA* is important for the diagnosis and disease progression monitoring of patients with AML [21]. In this study, using karyotyping, FISH and aCGH, three patients with t(8;16)(p11.2;p13.3) were typically analyzed. It is found that one male patient is pure t(8;16)(p11.2;p13.3), and two female patients have a similar additional chromosomal anomaly of 1q duplication. To the best of our knowledge, this is the first study of delineation of 1q duplication by aCGH in AML patients with t(8;16)(p11.2;p13.3).

Previous studies demonstrated that t(8;16)(p11.2;p13.3) is a rare recurrent cytogenetic abnormality associated with AML. AML patients with this abnormality often shows unique clinical and biological characteristics [22]. Compared to current categories t(15;17), t(8;21), inv(16) and t(11q23) in AML, t(8;16) is clustered close to t(11q23) sharing commonly expressed genes [15]. Xie et al. reported 15 adult AML cases with t(8;16)(p11.2;p13.3) including 13 women and 2 men, and further confirmed that t(8;16)(p11.2;p13.3) commonly exhibits monoblastic or myelomonocytic differentiation, and arises in patients with a history of cancer treated with cytotoxic therapies. Patients with *de novo* AML with t(8;16) or treatment-related AML with t(8;16) without adverse prognostic factors have a good outcome [14]. In this work, three adult AML patients with t(8;16)(p11.2;p13.3) including one man and two women were identified. Furthermore, two female patients with t(8;16)(p11.2;p13.3) belong to AML subtype M5.

Different methods are applied to detect common balanced translocations and the loss or gain of large chromosomal segments in AML. As an example, FISH is a targeted method that enhances analytical resolution to 300–800 kb and allows the analysis of interphase nuclei as well as metaphases [23]. FISH method with high sensitivity has been successfully used in the detection and monitoring of trisomy 8 in AML patients [24]. A rare t(8;17) chromosomal translocation was found by metaphase-FISH in a case of AML [25]. The translocation t(8;16)(p11.2;p13.3) disrupts *KAT6A* (also known as *MOZ* and *MYST3*) on 8p11 and *CREBBP* (also named *CBP*) on 16p13 resulting in a fusion of the two genes, the fusion in AML was detected in several studies. [20, 26–29]. In our work, t(8;16)(p11.2;p13.3)/*KAT6A-CREBBP* fusion was also detected among AML patients using FISH method.

Compared to the conventional cytogenetic analysis and FISH method, aCGH is an attractive method for the investigation of cancer genomes [30]. aCGH has higher resolution, simplicity, high reproducibility, shorter turnaround time and precise mapping of aberrations. Most importantly, it avoids the need for cell culture and dividing cells [31–33]. Furthermore, aCGH chromosomal analysis facilitates rapid detection of cytogenetic abnormalities previously undetectable by conventional cytogenetics [23]. aCGH analysis adds to the prognostic stratification of patients with AML. Compared to conventional detection method karyotyping, aCGH shows a higher sensitivity, and detects loss of 17p in AML patients [23]. Recurrent deletions of 5q, 17q11.2 (*NF1* gene) and 20q were observed in 30 elderly patients [34]. aCGH detected the chromosome 7 origin of the marker chromosome with deletions of 7p and 7q in children, adolescent and adult AML [35, 36]. In our investigation, we applied aCGH to characterize the origin of the additional chromosomal materials in two patients with t(8;16)(p11.2;p13.3). Therefore, we found the segments were both from chromosome 1q at similar cytobands.

Gain of chromosome 1q is often involved in chromosomal translocations. Patients with 1q duplication have demonstrated a wide range of multiple malformations such as mental retardation, macrocephaly, large fontanels, prominent forehead, broad flat nasal bridge, high-arched palate, retrognathia, low-set ears, and cardiac defects [37, 38]. More recent studies manifest that 1q gain is also related to a slice of solid tumors. For instance, the gain of 1q is well known as a poor prognostic biomarker of Wilms tumor [39], it plays an important role in predicting poor clinical outcome in patients with thyroid carcinoma as well[40]. Besides, patients with 1q duplication showed worse survival and high risk in acute lymphoid leukemia, Burkitt lymphoma, and myeloproliferative neoplasms [41–44]. Moreover, previous studies suggest that partial trisomy for the 1q impacts the prognosis of AML, the 1q duplication portends the evolution of disease progression in hematological malignancies as a sole anomaly or associated with other changes[45–47]. As a very rare abnormality in AML patients, t(8;16)(p11.2;p13.3) was seldom reported compared to other chromosomal aberrations. The actual effects of 1q duplication involved in AML patients with t(8;16)(p11.2;p13.3) need further research to delineate.

Conclusion

In summary, three of 1,824 AML patients with t(8;16)(p11.2;p13.3) were analyzed in this study. We further confirmed t(8;16)(p11.2;p13.3) with *KAT6A/CREBBP* fusion by FISH and characterized 1q duplication in

two female patients (AML subtype M5) of those three using aCGH method. Based on the published studies of t(8;16), combining with our investigation, we found that 1q duplication is common in AML patients with t(8;16)(p11.2;p13.3). We also suggest that 1q duplication may be an adverse prognostic factor in AML patients with these anomalies. The understandings of molecular cytogenetic data would contribute to the diagnosis and treatment evaluation of AML.

List Of Abbreviations

AML: Acute myeloid leukemia

aCGH: Array comparative genomic hybridization

FISH: Fluorescence in situ hybridization

APL: Acute promyelocytic leukemia

WCP: Whole chromosome painting

Declarations

Ethics approval and consent to participate

This study was approved by University of Oklahoma Institutional Review Board for the Protection of Human Subjects.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

M Liu and YR gathered clinical information and drafted the manuscript.YR, YK and M Liu performed routine cytogenetic analysis and participated in the interpretation of the results. M Li performed FISH analysis and participated in the interpretation of the results. XL supervised the FISH analysis and helped draft the manuscript. XWperformed CGH array analysis and helped draft the manuscript. LZ and SLconceived the study, participated in its design, and extensively reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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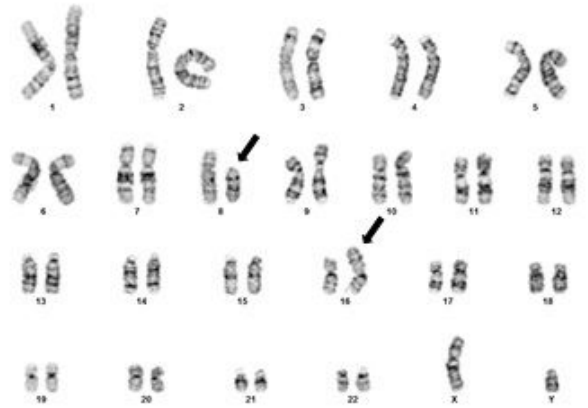
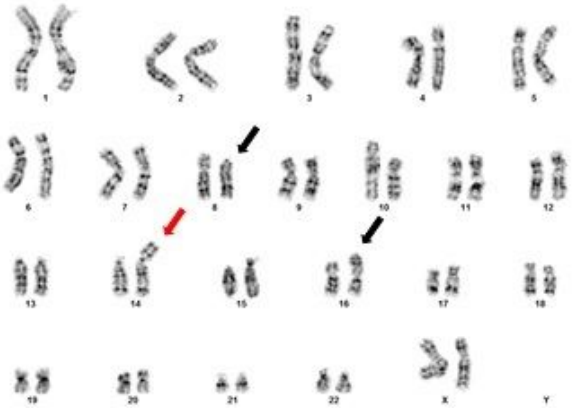
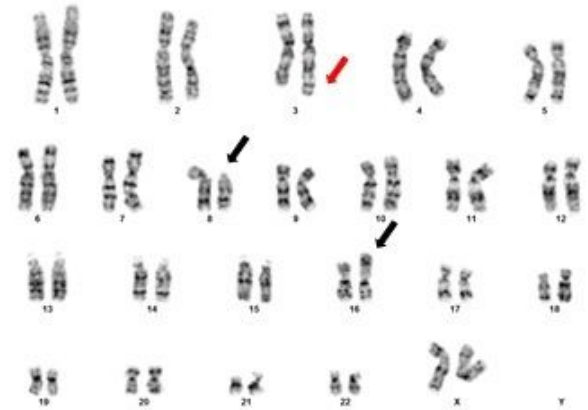
Figures



a. Patient 1



b. Patient 2



c. Patient 3

Figure 1

Representative abnormal karyotypes of three patients with t(8;16)(p11.2;p13.3). (a) Karyotype of patient No.1 showing 46,XY,t(8;16)(p11.2;p13.3) as a sole abnormality; (b) and (c) Karyotypes of patient No.2 and No.3 showing 46,XX,t(8;16)(p11.2;p13.3) and an additional chromosome segment attached to the short arm of chromosome 14 and the long arm of chromosome 3, respectively. Translocated derivatives 8 and 16 were indicated by black arrows, derivatives 14 and 3 were indicated by red arrows.

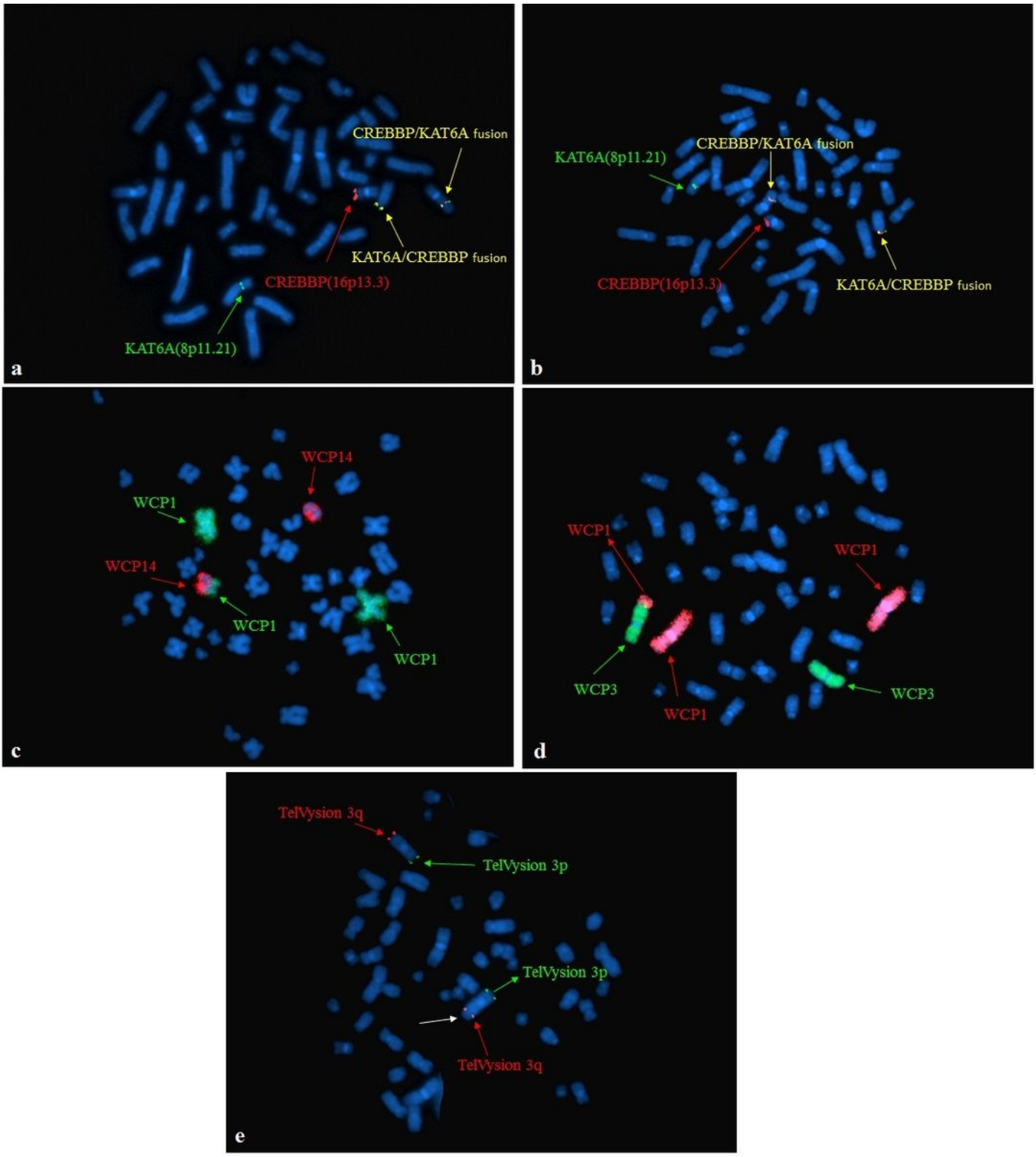
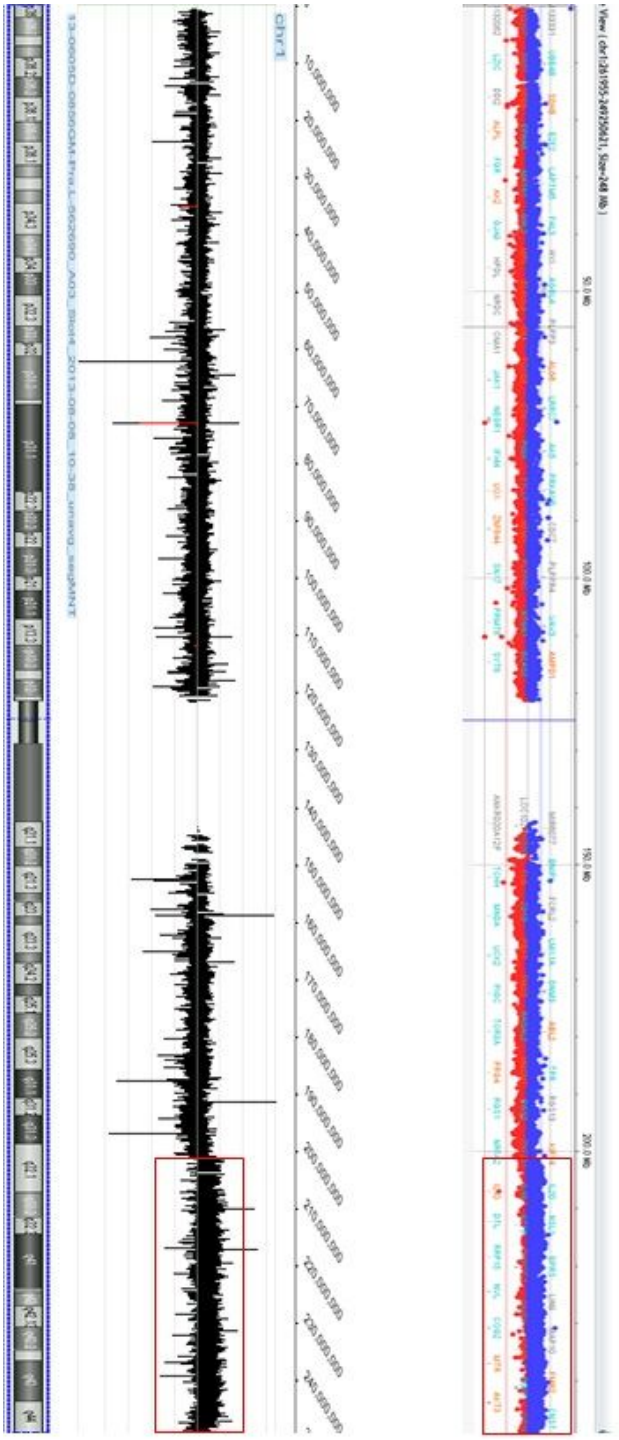


Figure 2

Metaphase FISH of patient No.2 (a) and No.3(b) showing KAT6A/CREBBP fusion signals. WCP FISH indicating the extra chromosomal materials on chromosome 14 and chromosome 3 both from chromosome 1 (c and d). No loss of the end portion of the long arm of chromosome 3 was indicated (e).



Patient No. 2 **Patient No. 3**

Figure 3

aCGH results of patient No.2 and patient No.3 showing partial 1q gain; duplicated 1q regions were indicated by red frames.